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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/818,939	03/28/2001	Gouzel Karimova	3495.0202	9624

22852 7590 02/11/2004

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EXAMINER	
SWOPE, SHERIDAN	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 02/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/818,939	KARIMOVA ET AL.	
	Examin r	Art Unit	
	Sheridan L. Swope	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *50-95* is/are pending in the application.

4a) Of the above claim(s) *57-93 and 95* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *50-56 and 94* is/are rejected.

7)☒ Claim(s) *50-56 and 94* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 March 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *0601* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's election with traverse of Invention I, Claims 50-56 and 94, as well as the species of adenylate cyclase from Claim 51 and the T25 and T18 fragments of Claim 53, which was received November 5, 2003, is acknowledged. The traversal is on the ground(s) that: "Claims 51 and 53 depend from claim 50. By definition, the subject matter of claims 51 and 53 is encompassed by claim 50. Thus, any adequate search of claim 50 necessarily must include an adequate search of each and every species encompassed by claims 51 and 53. Thus, searches of every species encompassed by claims 51 and 53 does not present a serious burden on the Office–or indeed any additional burden–and applicants are entitled to have the Office examine the full scope of claims 51 and 53." This argument is not found to be persuasive. Claim 50 is a generic linking claim that links the species of Claims 51 and 53. Claim 50 will be examined only to the extent that is encompassed by the elected species of Claims 51 and 53. The search for the elected species would not encompass the search for any other species of Claims 51 or 53 and searching all species would represent a burden on the Office. The requirement is still deemed proper and is therefore made FINAL.

Claims 57-93 and 95 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected Inventions, there being no allowable generic or linking claim. Claims 50-56 and 94 are examined on their merits.

Specification-Objections

The specification is objected to for the following reasons.

In Table 2, it is unclear what the headings "Clone", "Strand", "Osize", and "Phase" represent. It is requested that a legend for Table 2 be provided.

On page 1, line 13, "Karamora" should be corrected to "Karamova".

On page 21, line 16, it is unclear what is meant by "All XX positive clones...". Clarification is requested.

On page 28, paragraph 3, "n°" on lines 1, 1, and 4 should be corrected.

The abstract is objected to for not having a period (.) at the end.

Claims-Objections

Claims 50-56 and 94 are objected to for reciting non-elected subject matter.

Claim 50 is objected to for the following reasons:

i. Lacking an "and" on line 4: "...a first fragment of an enzyme;..." should be corrected to "...a first fragment of an enzyme; and...".

ii. The phrases "the said molecule" and "the said target ligand", on lines 9-10, should be corrected to "said molecule" and "said target ligand", respectively.

iii. The phrase "wherein signal amplification" on line 12 should be corrected to "wherein the signal amplification".

Claim 94 is objected to for the phrase "a first fragment a of an" on line 3, which should be corrected to "a first fragment of an".

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter.

See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 50-56 and 94 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-5, 7-9, and 47 of copending Application No. 10/240,102. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 51-53, 55, and 56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claim 55, the phrase "the calmodulin", on line 2, lacks antecedent basis and, therefore, is indefinite. In Claims 51, 53, and 56 the specific polynucleotide and polypeptide sequences referred to by "CyaA" are not disclosed by either the specification or the claims and, therefore, Claims 51, 53, and 56 are indefinite. For purposes of examination, it assumed that said polynucleotide and polypeptide have the sequence set forth and encoded by NCBI Accession Number NP_879578.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 50-56 and 94 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The invention employs novel cells, BTH101 and DHM1. Since the cells are essential to the claimed invention, they must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The enablement requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the cells. It is noted that applicants have deposited the organisms (pgs 15-16) but there is no indication in the specification as to public availability. If the deposit was made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the specific strain has been deposited under the Budapest Treaty and that the strain will be irrevocably and without restriction or condition released to the public upon the issuance of the patent, would satisfy the deposit requirement made herein.

If the deposit has not been made under the Budapest treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, applicants may provide assurance or compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

1. during the pendency of this application , access to the invention will be afforded to the Commissioner upon request;

2. all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

3. the deposit will be maintained in a public repository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer; and

4. the deposit will be replaced if it should ever become inviable.

Claims 50-52, 54-56 and 94 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a signal amplification system comprising a first peptide comprising the T25 fragment of CyaA linked to a molecule of interest and a second peptide comprising the T18 fragment of CyaA linked to a target ligand, wherein the amplification is performed in BTH101 and DHM1 cells, does not reasonably provide enablement for any signal amplification system comprising a first peptide comprising any fragment of any enzyme, or any fragment of any adenylate cyclase, linked to a molecule of interest and a second peptide comprising any fragment of any enzyme, or any fragment of any adenylate cyclase, or any modulating substance thereof, linked to a target ligand. Furthermore, the specification is not enabling for said amplification system further comprising any mutant of the enzyme fragment within said first peptide, any mutant of the CyaA fragment within said first peptide, or any substance capable of stimulating or inhibiting the interaction between a target ligand and a molecule of interest. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 50, 54, and 94 are so broad as to encompass a system comprising a first peptide comprising any fragment of any enzyme linked to a molecule of interest. Claims 51 and 52 are so broad as to encompass a system comprising a first peptide comprising any fragment of any adenylate cyclase linked to a molecule of interest. Claims 50, 54-56, and 94 are so broad as to

encompass a system comprising a second peptide comprising any fragment of any enzyme, or any modulating substance thereof. Claims 51 and 52 are so broad as to encompass a system comprising a second peptide comprising any fragment of any adenylate cyclase, or any modulating substance thereof. Claim 55 is so broad as to encompass a system comprising any mutant of any enzyme fragment within said first peptide. Claim 56 is so broad as to encompass a system comprising any mutant of any CyaA fragment within said first peptide. Claim 94 is so broad as to encompass a system further comprising any substance capable of stimulating or inhibiting the interaction between a target ligand and a molecule of interest. The scope of each of these claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polynucleotides broadly encompassed by the claim.

Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which enzymes and fragments thereof can be used in the recited system and which changes can be tolerated in said enzymes and fragments thereof and obtain the desired amplification system requires a knowledge of and guidance with regard to which enzymes and fragments thereof may be useful and which amino acids in the enzymes' sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which each enzyme's structure relates to its function. However, in this case the disclosure is limited to a signal amplification system comprising a first peptide comprising the T25 fragment of CyaA linked to a molecule of interest and a second peptide comprising the T18 fragment of CyaA linked to a target ligand.

While enzyme screening methods as well as recombinant and mutagenesis techniques are known, it is not routine in the art to screen multiple enzymes, multiple fragments thereof, or

multiple substitutions or multiple modifications in said enzymes and fragments, as encompassed by the instant claims, and the positions within a enzyme's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any enzyme and the results of such modifications are unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given enzyme to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of Claims 50-52, 54-56 and 94 which, encompasses a signal amplification system comprising a first peptide comprising any fragment of any enzyme, or any fragment of any adenylate cyclase, linked to a molecule of interest and a second peptide comprising any fragment of any enzyme, or any fragment of any adenylate cyclase, or any modulating substance thereof, linked to a target ligand. Neither does the specification support the broad scope of Claims 55, 56, or 94 wherein said amplification system further comprises any mutant of any enzyme fragment within said first peptide, any mutant of any CyaA fragment within said first peptide, or any substance capable of stimulating or inhibiting the interaction between a target ligand and a molecule of interest, respectively. The specification does not support the broad scope of Claims 50-52, 54-56 and 94 because the specification does not establish: (A) any enzymes, other than CyaA, that can be successfully used in the recited system; (B) any fragments of any enzymes, other than T25 and T18 of CyaA, that can be successfully used in the recited system; (C) regions of any fragment of any enzyme which may be modified without effecting the utility of said fragments in the recited system; (D) the general tolerance of the utility of any fragment of any enzyme to modification and extent of such tolerance; (E) any substance capable of stimulating or inhibiting the interaction between

any target ligand and any molecule of interest; (F) a rational and predictable scheme for choosing any enzyme, fragments thereof, and variants thereof as well as modulators of the interaction between any target protein and any protein of interest with an expectation of obtaining the desired utility; and (G) the specification provides insufficient guidance as to which of the essentially infinite possible choices of enzymes, fragments thereof, and variants thereof, as well as modulators of interaction between any target protein and any protein of interest that are likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of signal amplification systems comprising a first peptide comprising any fragment of any enzyme, or any fragment of any adenylate cyclase, linked to a molecule of interest and a second peptide comprising any fragment of any enzyme, or any fragment of any adenylate cyclase, or any modulating substance thereof, linked to a target ligand. In addition, the specification is not enabling for said amplification system further comprising any mutant of any enzyme fragment within said first peptide, any mutant of any CyaA fragment within said first peptide, or any substance capable of stimulating or inhibiting the interaction between a target ligand and a molecule of interest. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of sequences having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 50-52, 54-56 and 94 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to a genus of amplification systems comprising a first peptide comprising any fragment of any enzyme, or any fragment of any adenylate cyclase, linked to a molecule of interest and a second peptide comprising any fragment of any enzyme, or any fragment of any adenylate cyclase, or any modulating substance thereof, linked to a target ligand. Said genus also encompasses said amplification system further comprising any mutant of any enzyme fragment within said first peptide, any mutant of any CyaA fragment within said first peptide, or any substance capable of stimulating or inhibiting the interaction between a target ligand and a molecule of interest. The specification teaches the structure of only a single representative species of such systems: the CyaA system using the T25 and T18 fragments. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of being a signal amplification system in BTH101 and DHM1 cells. Given this lack of description of representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Sheridan Lee Swope, Ph.D.

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1800~~ 1600